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13. ABSTRACT ***(Maximum 200 Words)*** In the final year of this grant, we are completgeing an experiment in which aged monkeys are assessed for levodopa-induced dyskinesias and given a fluorodopa PET scan. They then receive lenti-GDNF under the control of the tetracycline promoter. Three months following lenti-GDNF, they are again assessed for levodopa-induced dyskinesias and given a fluorodopa PET scan. Then half of the aged monkeys receive tetracycline to shut of the GDNF expression in vivo. Monkeys are assessed for levodopa-induced dyskinesias and given a fluorodopa PET scan 3 and 6 months later. This study will determine whether we can control gene expression in vivo and make gene therapy safe for clinical use.

14. SUBJECT TERMS:
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4) Introduction

Parkinson's disease (PD) is a chronic neurodegenerative disorder that affects over 1,000,000 Americans. Symptoms include tremor, bradykinesia and rigidity, all of which invariably increase in severity as the disease progresses. Pathologically, there is progressive loss of striatal dopamine and degeneration of dopaminergic neurons within the substantia nigra pars compacta. Palliative symptomatic treatment can be achieved by dopamine (DA) replacement therapy using the dopamine precursor, levodopa. However, "wearing off effects" with disabling dyskinesias complicates symptomatic treatments. As PD progresses, motor and nonmotor symptoms emerge which are not responsive to levodopa. Since treated patients show a life expectancy similar to age-matched controls, patients can survive with crippling symptoms for many years. Thus, new innovative treatment strategies are needed to sustain the quality of life for these individuals. Recently, surgical treatment strategies such as neural transplantation (e.g. 1), pallidotomy (e.g. 2) or deep brain stimulation (e.g. 3) have gained considerable attention for the treatment of PD. However, preventing neuronal degeneration, rather than replacing neurons or disrupting basal ganglia circuitry may be a more parsimonious way of sustaining nigrostriatal and clinical function in patients with PD. The present proposal examined anew study in aged nonhuman primates that serve as a follow-up to our recent publication in Science demonstrating the ability of lentiviral delivery of the trophic factor GDNF to prevent degeneration and enhance nigrostriatal function in nonhuman primate models of Parkinson's disease. In this new study, we will determine whether we can control transgene expression using the tet-off system.

5) Body of Report

Control of transgene expression in nonhuman primate models of PD: We previously demonstrated that lentivirally-delivered GDNF provides potent function, neuroanatomical, and neurochemical effects on the degenerating nonhuman primate nigrostriatal system (see previous

progress reports and Kordower et al., 2000). In fact, lenti-GDNF was so potent that some parameters displayed hyperdopaminergic function. Prior to going to clinical trials, it is essential that we have control of the GDNF expression in vivo. In this regard, we have designed the following experiment. Ten aged Rhesus monkeys comprise this experiment. They were evaluated for baseline levels of levodopa-induced dyskinesias and received a fluorodopa PET scans. Then they all received a series of unilateral intrastriatal injections of lenti-GDNF under the control of the tetracycline promoter. Half the animals received tetracycline while the others did not. Three months later they were evaluated for levodopa-induced dyskinesias, testing the hypothesis that lenti-GDNF mediated increases in the number of terminals will move the dyskinesia dose response profile to the left (fewer dyskinesias) and determine empirically that increasing dopaminergic tone in this way does not increase the expression of dykinesias. These monkeys will also got a second fluorodopa PET scan. The monkeys receiving the lenti-GDNF that was "on" displayed an increase in fluorodopa uptake on the side of the side of the treatment. The monkeys receiving the "off" did not. Then half of the animals Now the groups have been switched. The monkeys receiving the "off" lenti-GDNF are now on and the monkeys receiving the "on" GDNF are now off. . Both 3 and 6 months later, the monkeys will again be tested for levodopa-induced dyskinesias and receive PET scans. We hypothesize that the "tet" exposed animals will reverse the expression of levodopa-induced dyskinesias and reverse the increase in fluorodopa on PET. These experiments will establish the controllability of gene expression making this procedure safe for clinical trials. This experiment will continue through the final year of funding.

6) Key Research Accomplishments

Establishing whether we can control gene expression of GDNF in aged nonhuman primates.

7) Reportable Outcomes

none but there will be published reports following the analysis of the above data.

8) Conclusions: We cannot at present make any definitive conclusions as we are completing still completing the experiments

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11: Appendices: None

12: Bibliography and Personnel:

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